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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,493	ARNAOUT ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-45* is/are pending in the application.

4a) Of the above claim(s) *13 and 15-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/6/01, 4/10/02,* 1/6/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 13-45 are pending.

2. Applicant's election without traverse of Group III, claims 14 drawn to a polypeptide of CD11b α comprising amino acids 144-332 wherein the Ile at position 332 has been replaced by an amino acid selected from the group consisting of Gly and Ala filed on 12/27/04, is acknowledged.

Upon reconsideration Examiner has extended the search to cover all the species recited in claim 14.

3. Claims 13 and 15-45 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claim 14 is under examination as it reads on a polypeptide of CD11b α subunit (a) having the Ile at position 332 replaced with an amino acid selected from the group of Gly and Ala, (b) a polypeptide comprising amino acids 144 to 332 of CD11b α subunit wherein the Ile at position 332 has been replaced by an amino acid selected from the group consisting of Gly and Ala. (c) a polypeptide comprising amino acids 144 to 331 of CD11b α subunit, the polypeptide not comprising amino acids 332 to 1152 of CD11b α subunit; (d) a polypeptide comprising amino acids 144 to 320 of CD11b α subunit wherein the phe a tamino acid 313 and the Ala at amino acid 320 have been replaced by Cys; (e) a polypeptide comprising amino acids 144-30 of CD11 b a subunit wherein the Val at amino acid 315 and the Ala at amino acid 320 have been replaced by Cys.

4. Applicant's IDS, filed 11/26/01, 4/10/02 and 01/06/03, is acknowledged.

5. The amendment filed 2/20/02, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The preliminary amendment filed on 2/20/02 to the to FIG.2A and FIG.2B of the drawings substituting original Fig.2A and Fig.2B with a new FIG.2A and Fig.2B, respectively represents a departure from the specification and the claims as originally filed. The new electron density map of the C-terminal portions of α7 from $11bA^{123-321}$ structure is different than the originally filled electron density map. The specification and the claims as originally filed have no support for the new replacement of electron density map of the C-terminal portions of α7 from $11bA^{123-321}$ structure.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 14 is indefinite and ambiguous in the recitation of:

i. "a CD11b a subunit polypeptide having the Ile at position 332 replaced with an amino acid selected from the group consisting of Gly and Ala",

ii. "a polypeptide comprising amino acids 144 to 332 of CD11b α subunit wherein the Ile at position 332 has been replaced by an amino acid selected from the group consisting of Gly and Ala",

iii. "a polypeptide comprising amino acids 144 to 331 of CD11b α subunit, the polypeptide not comprising amino acids 332 to 1152 of CD11b α subunit",

iv. "a polypeptide comprising amino acids 144 to 320 of CD11b α subunit wherein the phe a tamino acid 313 and the Ala at amino acid 320 have been replaced by Cys",

v. "a polypeptide comprising amino acids 144-320 of CD11b α subunit wherein the Val at amino acid 315 and the Ala at amino acid 320 have been replaced by Cys",

vi. " a CD11b α subunit polypeptide having the Ile at position 332 replaced with an amino acid other than Ile", and

vii. "a polypeptide comprising amino acids 144 to 332 of CD11b α subunit wherein the Ile at amino acid 332 has been replaced by an amino acid other than Ile".

Recitation of amino acid position of a protein without providing SEQ ID NO for the protein is indefinite and ambiguous because different laboratories may have different numbering of the same protein. It is unclear whether amino acids refer to mature or immature CD11b α. It is unclear whether the CD11b α is a 1137, 1153 amino acid sequence. For Example, Xiong *et al* (IDS ref. No. AQ) teach that the modified integrin CD11b A domain at Ile316→Gly in the mature protein (see page 5, last sentence), while the same Ile would be at amino acid position 332 in immature form.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 14 is rejected under 35 U.S.C. 11 2, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases:

A. "a polypeptide comprising amino acids 144 to 320 of CD11b α subunit wherein the phe at amino acid 313 and the Ala at amino acid 320 have been replaced by Cys", and

B. "a polypeptide comprising amino acids 144-320 of CD11b α subunit wherein the Val at amino acid 315 and the Ala at amino acid 320 have been replaced by Cys"'

claimed in claim 14(d-e) represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 7/3/03 and 6/23/04 does not point to the specification for support for the newly added limitation "a polypeptide comprising amino acids 144 to 320 of CD11b α subunit wherein the phe a tamino acid 313 and the Ala at amino acid 320 have been replaced by Cys" and a polypeptide comprising amino acids 144-320 of CD11b α subunit wherein the Val at amino acid 315 and the Ala at amino acid 320 have been replaced by Cys" as claimed in claim 14. However, the specification does not provide a clear support of said limitations. It is noted that SEQ ID NO: 1 is the A domain C144-334 of full-length human CD11b α subunit of GenBank Accession No. RWHU1B. The instant claim now recites a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

10. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a CD1b α subunit polypeptide having the Ile at position 332 replaced with an amino acid selected from the group consisting of Gly and Ala in claim 14(a), a polypeptide "comprising" amino acids 144 to 332 of CD11b α subunit wherein the Ile at position 332 has been replaced by an amino acid selected from the group consisting of Gly and Ala in claim 14(b), a polypeptide "comprising amino acids 144-331 of CD11b a subunit, the polypeptide not comprising amino acids 332-1152 of CD11b α subunit in claim 14(c), a polypeptide "comprising" amino acids 144 to 320 of CD11b α subunit wherein the Phe at amino acid 313 and the Ala at amino acid 320 have been replaced by Cys in claim

14(d), a polypeptide "comprising" amino acids 144 to 320 of CD11b α subunit wherein the Val at amino acid 315 and the Ala at amino acid 320 have been replaced by Cys in claim 14(e), a CD11b α subunit polypeptide having the Ile at position 332 replaced with an amino acid other than Ile in claim 14(e) and a polypeptide comprising amino acids 144 to 332 of CD11b α subunit wherein the Ile at amino acid 332 has been replaced by an amino acid other than Ile in claim 14(g). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to how to make any CD11b α subunit, wherein the specification fails to provide a structure for the CD11b α subunit.

It is unclear form the specification as to the relationship between amino acid numbering of Ile^{316} and Ile^{332}. The specification on page 7, discloses that Table 2 and 3 refer to the numbering in the complete protein (including 16 aa signal sequence). It appears that Ile^{316} corresponds to the incomplete human CD11b and the Ile^{332} corresponds to the complete human CD11b subunit. Therefore, it appears that Ile^{316} and Ile^{332} are the same amino acid residue of the human CD11b. The specification on page 11, under Example 2, discloses that an A-domain with an Ile to glycine substitution ($11bA^{I\rightarrow G}$) exhibited a "high affinity" state (open conformation). Further the same substitution created in the holoreceptor dramatically increased its ligand binding activity. Furthermore, the specification discloses that "open" high affinity conformation is primarily dictated by an Ile-based switch, intrinsic to the domain and acting allosterically to regulated ligand binding affinity on the MIDAS face. However, the specification is silence with respect to the amino acid substitutions claimed in claim 14(d-e). There is no guidance in the specification as what affinity state the substitutions in amino acids $313^{F\rightarrow C}$ and $320^{A\rightarrow C}$ claimed in claim 14(d) or $315^{V\rightarrow C}$ and $320^{A\rightarrow C}$ claimed in claim 14(e) would exhibit.

The term "comprising" in claim 14 is an open-ended. It would open the claimed 144 to 332, 144 to 331 and 144 to 320 fragments to include addition non-specified amino acids on either or both sides of the N- or C termini of the fragments. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for a "high affinity" state polypeptide that increase ligand binding affinity.

Further, claim 14(f-g) recites "the Ile at amino acid 332 has been replaced by an amino acid other than Ile", however, there is tremendous variability in the importance of individual amino acids in protein sequences. Since the A domain is a key determinants of activity of CD11b α subunit, residue substitutions that are conservative (e.g., Glu in equilibrium Asp, Asn in equilibrium Asp, Ile in equilibrium Leu, Lys in equilibrium Arg and Ala in equilibrium Gly) can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. Therefore, one skill in the art would not be able to predicted what residue substitutions can replace Ile at position 332 of CD11b α subunit besides Gly and Ala. For Example, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid

sharply reduced the biological activity of the mitogen.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies such CD11b α subunit. There is nothing in the claim, which establishes the structure of which polypeptides that can be used to make the variants. It is unclear what species of CD11b α subunit polypeptide is derived from (i.e. human, mouse, rat, among others). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of CD11b α subunit broadly encompassed by the claims. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. For Example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Applicant has not enabled structurally related and unrelated compounds comprising "amino acids 144 to 332" or "SEQ ID NO:1" which would be expected to have greater differences in their biological activities. There is insufficient direction or objective evidence as to how to make and to how to use any polypeptide of CD11b α subunit, and in turn how to obtain the Ile^{332}, Phe^{313}, Ala^{320}, Val^{315} variant thereof. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The incorporation of essential material in the specification by reference to GenBank Accession No. RWHU1B is improper since the incorporation by reference is not in compliance with 37 CFR 1.57. Essential material to be incorporated would require specific trigger language: "incorporated by reference".

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a CD1b α subunit polypeptide having the Ile at position 332 replaced with an amino acid selected from the group consisting of Gly and Ala in claim 14(a), a polypeptide "comprising" amino acids 144 to 332 of CD11b α subunit wherein the Ile at position 332 has been replaced by an amino acid selected from the group consisting of Gly and Ala in claim 14(b), a polypeptide "comprising amino acids 144-331 of CD11b a subunit, the polypeptide not comprising amino acids 332-1152 of CD11b α subunit in claim 14(c), a

polypeptide "comprising" amino acids 144 to 320 of CD11b α subunit wherein the Phe at amino acid 313 and the Ala at amino acid 320 have been replaced by Cys in claim 14(d), a polypeptide "comprising" amino acids 144 to 320 of CD11b α subunit wherein the Val at amino acid 315 and the Ala at amino acid 320 have been replaced by Cys in claim 14(e), a CD11b α subunit polypeptide having the Ile at position 332 replaced with an amino acid other than Ile in claim 14(e) and a polypeptide comprising amino acids 144 to 332 of CD11b α subunit wherein the Ile at amino acid 332 has been replaced by an amino acid other than Ile in claim 14(g).

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (CD11b α subunit) to describe the claimed genus, nor does it provide a description of structural features that are common to species (CD11b α subunit). As discussed above, the specification provides no structural description of CD11b α subunit other than the one disclosed in GenBank Accession No. RWHU1B; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed human CD11b looks like. The specification's disclosure is inadequate to describe the claimed CD11b α subunit.

Applicant has disclosed only the amino acids of GenBank Accession No. RWHU1B (improperly incorporated by reference); therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claim 14 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-50 of copending Application No. 09/805,354. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to the same polypeptides comprising all or part of a variant of CD11 α subunit A domain of amino acids 144-332. The crucial isoleucine (Ile) residue at position 332 is absent in the instant application and the `354 application. Further, the Ile can be either deleted or replaced with different amino acids residue such as Ala or Gly in both applications. It is noted that SEQ ID NO: 1 recited in claim 50 of `354 application is the A domain of CD11b α subunit and the Ile at amino acid 189 corresponds to the Ile 332 of the full-length CD11b a subunit claimed in claim 14 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claim14 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-19 of copending Application No. 10/144,259. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to the same polypeptides comprising all or part of a variant of CD11 α subunit A domain of amino acids 144-332. The crucial isoleucine (Ile) residue at position 332 is absent in the instant application and the `259 application. Further, the Ile can be either deleted or replaced with different amino acids residue such as Ala or Gly in both applications. It is noted that SEQ ID NO: 30 recited in claims 17 and 19 of `259 application is the full-length CD11b α subunit claimed in claim 14 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 21, 2005

Maher Haddad

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